UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/818,066	03/27/2001	Shuping Tong	00786-287004 / MGH-0960.3	1622

7590 05/21/2002

JANIS K. FRASER
Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804

EXAMINER
BRUMBACK, BRENDA G

ART UNIT	PAPER NUMBER
1642	8

DATE MAILED: 05/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/818,066	TONG ET AL.	
	Examiner	Art Unit	
	Brenda G. Brumback	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The Preliminary Amendment filed 08/02/01 is acknowledged. Claims 1-9 are pending and under examination.

Information Disclosure Statement

The Information Disclosure Statement filed 03/27/01 and the Supplemental Information Disclosure Statement filed 09/27/01 have been considered. Signed copies of the PTO-1449 forms are attached hereto.

Specification

The use of the trademarks SEPHADEX, GIGAPACK, and AMPLIFY has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 6 are drawn to a polypeptide consisting of a first amino acid sequence that is identical to amino acids (aa) 1-104 or aa 25-161 of a naturally occurring hepadnavirus pre-S protein or a fragment thereof which includes at least aa 80-102 or at least aa 98-161 of the naturally occurring pre-S

protein. The metes and bounds of the claimed polypeptide cannot be determined because it is unclear what specific sequences they are based upon. While the specification discloses two examples of amino acid sequences of pre-S proteins, it is unclear whether either or both of these are the sequences of the claimed pre-S protein sequences or if other undisclosed sequences are also encompassed.

Claims 5 and 9 recite the amino acid sequence of glutathione S-transferase; however, the metes and bounds of the claims cannot be ascertained absent specific recitation of the specific sequence of glutathione S-transferase encompassed within the claims or in the alternative reference in applicant's disclosure to a sequence for glutathione transferase which is disclosed in the prior art.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a "written description" rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Vas-Cath Inc. V. Mahurka, 19 USPQ2d 1111, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the "written description" inquiry, is *whatever is now claimed*" (see page 1117).

A review of the language of the claim indicates that these claims are drawn to a genus, i.e., the genus of polypeptides consisting of portions of any naturally occurring hepadnavirus pre-S protein with one or more heterologous sequences. A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural

features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention".

There are two species of the claimed genus disclosed that are within the scope of the claimed genus, *i.e.* polypeptides comprising either the pre-S protein sequences of one particular strain of hepatitis B virus (HBV) or one particular strain of duck hepatitis B virus (SHBV) with glutathione S-transferase. The disclosure of one or two species may provide an adequate written description of a genus when the species disclosed are representative of the genus. However, the present claim encompasses numerous species that are not further described. There is substantial variability among the species.

One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus of polypeptides which comprises pre-S protein sequences from all strains of naturally occurring hepadnaviruses with a heterologous sequence or sequences. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (see *Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claims 1-9 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polypeptides consisting of aa sequences corresponding to the aa sequence of the HBV or DHBV pre-S proteins with glutathione transferase which are disclosed in applicant's specification, does not reasonably provide enablement for polypeptides consisting of aa sequences corresponding to other naturally occurring hepadnaviruses with any heterologous sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of

the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claimed invention is drawn to a polypeptide consisting of a first amino acid that is identical to any naturally occurring hepadnavirus pre-S protein and one or more heterologous amino acid sequences.

The state of the prior art and the predictability or lack thereof in the art: The art teaches that the amino acid sequences of naturally occurring hepatitis B viruses are highly variable with escape mutants having changes in the aa sequence of the surface antigen frequently occurring (see Minuk, G., Canadian Journal of Gastroenterology 16/1:45-54, January 2002, the abstract, and Weingerger et al., Journal of General Virology 81, pt.5:1165-74, May 2000, the abstract).

The amount of direction or guidance present and the presence or absence of working examples: Given the teachings of unpredictability regarding the variability of the aa sequences of naturally occurring hepadnavirus pre-S proteins which are found in the art, detailed teachings are required to be present in the disclosure to enable the skilled artisan to make and use polypeptides corresponding to aa 1-104 or aa 25-161 of any naturally occurring hepadnavirus pre-S protein. Such teachings are absent. The specification discloses the sequences of the pre-S proteins for a single strain of HBV and for a single strain of DHBV. There is no disclosure of any pre-S sequences for any other strains or for any naturally occurring escape mutants.

The breadth of the claims and the quantity of experimentation needed: Given the teachings of unpredictability found in the art regarding the variability in the aa sequence of the pre-S proteins in naturally occurring hepadnaviruses and in the absence of sufficient disclosure in applicant's specification to overcome the teachings of unpredictability which are found in the art, it would require undue experimentation by one of skill in the art to be able to make and use the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 103

Claims 1 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cabezon et al. (EPA 0 278 940).

The claimed invention is drawn to a polypeptide consisting of a first amino acid sequence that is identical to either aa 1-104 or aa 25-161 of a naturally occurring hepadnavirus pre-S protein, or fragments thereof to include either aa 80-102 or aa 8-161 respectively, and a second heterologous sequence.

Cabezon et al. teach polypeptides corresponding to the pre-S1 and pre-S2 regions of HBV. Cabezon teach that for the particular strain disclosed, the pre-S polypeptide is 163 aa in length, with the pre-S1 polypeptide corresponding to aa 1-108 and the pre-S2 polypeptide corresponding to aa 109-163 (see page 1, lines 30-41). Cabezon et al. teach the HBV polypeptides fused with one or more heterologous sequences for preparation of vaccine compositions (see the abstract and second full paragraph under *Summary of the Invention*). Absent some evidence to the contrary, the polypeptides disclosed by Cabezon are obvious variants of the polypeptides of the claimed invention.

Claims 5 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cabezon et al. in view of Khudyakov et al. (Journal of Virology, 68/11:7067-74, November 1994).

The claimed invention is as described *supra*, wherein the heterologous aa sequence is glutathione S-transferase.

As set forth *supra*, Cabezon et al. teach polypeptides sequences corresponding to aa 1-108 or aa 109-163 of the HBV pre-S protein fused with one or more heterologous sequences. Cabezon et al. do not teach the heterologous sequence as glutathione S-transferase.

Khudyakov et al. teach fusion polypeptides comprising glutathione S-transferase and antigenic epitopes of hepatitis E virus expressed in E. coli.

One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have expressed the polypeptides disclosed by Cabezon et al. fused with glutathione S-transferase according to the teachings of Khudyakov et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do so as a convenient and efficient means of recombinantly producing HBV pre-S antigens for immunotherapeutic or immunodiagnostic applications.

Conclusion

Claims 2-4, 7, and 8 are free of the prior art.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Anthony Caputa whose telephone number is (703) 308-3995. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1642 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Official FAX telephone number is (703) 872-9306 and the After Final FAX telephone number is (703) 872-9307. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

Brenda Brumback
Patent Examiner